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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Bannon, et al. Examiner: Huynh, P.
Serial No.: 09/478,668 Art Unit: 1644
Filed: January 6, 2000 Group: 1640
For: METHODS AND REAGENTS FOR DECREASING CLINICAL REACTIONS
TO ALLERGY

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APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Applicant appeals to the Board of Patent Appeals and Interferences (the "Board") from the Examiner's rejection of claims 37-71. A Notice to this effect was filed pursuant to 37 C.F.R. § 1.191(a) on November 7, 2002. The stamped return postcard that was filed with the Notice has been received by Applicant indicating that the Notice was received by the Patent and Trademark Office on November 12, 2002.

Filed herewith is a Petition under 37 C.F.R. § 1.136 for a five (5) month extension of time, from January 12, 2003, up to and including June 12, 2003, to file this Appeal Brief (the "Brief"). Pursuant to 37 C.F.R. § 1.192(a), this Brief is being filed in triplicate.

Also enclosed are checks to cover the \$985.00 fee under 37 C.F.R. § 1.17(a)(5) for the Petition and the \$160.00 fee under 37 C.F.R. § 1.17(c) for the Appeal Brief. Please charge any additional fees (or credit any overpayment), to our Deposit Account 03-1721.

Real Parties in Interest

As a result of assignments by the inventors in parent application U.S. Serial No. 09/141,220 filed August 27, 1998, the real parties in interest in this application are the University of Arkansas ("UArk"), SEER Pharmaceuticals LLC (f/k/a Panacea Pharmaceuticals, LLC), and the Mt. Sinai School of Medicine of the City University of New York ("Mt Sinai"). An assignment from inventors Garry Bannon and Wesley Burks to UArk was recorded in the Patent and Trademark Office on April 23, 1999 at Reel 010065, Frame 0008. An assignment from

inventor Howard Sosin to Panacea Pharmaceuticals, LLC was recorded in the Patent and Trademark Office on August 26, 1999 at Reel 010190, Frame 0516. A Certificate of Amendment changing the name of Panacea Pharmaceuticals, LLC to SEER Pharmaceuticals, LLC was filed with the Secretary of State of the State of Delaware on October 25, 2002. An assignment from inventor Hugh Sampson to Mt Sinai was recorded in the Patent and Trademark Office on October 22, 1998 at Reel 009539, Frame 0550.

Related Appeals and Interferences

No other pending appeals or interferences are known to Appellant, Appellant's legal representative, or Appellant's assignee that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no such pending appeals or interferences are known that may have a bearing on the Board's decision in this appeal. However, Appellant expects to file Appeal Brief's for co-pending applications U.S. Serial No. 09/455,294 filed December 6, 1999 and U.S. Serial No. 09/731,375 filed December 6, 2000 addressing some issues that overlap with the issues presented here.

Status of Claims

The application was filed with claims 1-36. Claims 1-13 were cancelled in a Preliminary Amendment filed January 6, 2000. Claims 14-36 were the subject of a Restriction Requirement mailed July 31, 2000. Claims 30-36 were cancelled September 29, 2000 in response to the Restriction Requirement. Claims 14-29 were examined in an Office Action mailed June 19, 2001. Claims 14-29 were canceled in an Amendment filed September 19, 2001; claims 37-59 were added. Claims 37-59 were finally rejected in an Office Action mailed December 18, 2001. Claims 37-42, 46-47, 51 and 53 were amended in an Amendment filed June 18, 2002; claims 60-71 were added; and continued examination was requested under 37 C.F.R. § 1.114. Claims 37-71 were rejected in an Office Action mailed September 30, 2002. Thus, claims 37-71 are pending and stand rejected. The rejection of claims 37-71 is hereby appealed. A listing of pending claims 37-71 is provided as **Attachment I**.

Status of Amendments

This Brief is being submitted together with an Amendment that cancels claims 52 and 54-59 and amends claims 61-62 to correct an issue of antecedent basis. A copy of claims 37-51, 53

and 60-71 that will be pending after entrance of the Amendment is provided as **Attachment II**. For the purpose of this Brief, Appellant is assuming that the Amendment will be entered since the claim amendments found therein simplify the issues under appeal. In particular, all rejections of claims 52 and 54-59 are rendered moot and the antecedent basis in claims 61-62 is corrected. Accordingly, in the following the issues on appeal will be discussed as if they applied to the claims that will be pending *after* entrance of the Amendment.

Summary of Invention

The present invention is directed to modified protein allergens. A modified protein allergen has an amino acid sequence that is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope. As a consequence of the modification, IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen.

Issues

The issues on appeal are:

- (1) Are claims 37-51, 53 and 60-71 invalid for lack of enablement?
- (2) Are claims 37-51, 53 and 60-71 invalid for lack of written description?
- (3) Are claims 65-69 invalid for containing new matter?
- (4) Are claims 37, 60 and 63 indefinite for reciting the term "substantially"?
- (5) Are claims 37-39, 41-46, 48-51 and 53 anticipated by U.S. Pat. No. 5,547,669?
- (6) Are claims 37, 60-61 and 63-71 anticipated by Burks et al. (1997)?
- (7) Are claims 37 and 47 obvious in light of U.S. Pat. No. 5,547,669 and Hoyne et al.?
- (8) Is claim 37 obvious in light of U.S. Pat. No. 5,547,669 and Burks et al. (1994)?
- (9) Are claims 60-62 obvious in light of U.S. Pat. No. 5,547,669 or Burks et al. (1997) each in combination with U.S. Pat. No. 5,449,669?

Grouping of Claims

- (1) Claims 37-51 and 65-71 stand or fall together.
- (2) Claim 53 stands or falls alone.
- (3) Claims 60-62 stand or fall together.
- (4) Claims 63-64 stand or fall together.

Argument

Claims 37-51, 53 and 60-71 are not Invalid for Lack of Enablement

Claims 37-51, 53 and 60-71 stand rejected for lack of enablement (see heading # 4 in the Office Action mailed September 30, 2002). In supporting this rejection, the Examiner cites *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and states that the disclosure in the specification is insufficient to enable one skilled in the art to practice the broader claimed invention without an undue amount of experimentation. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

As acknowledged by the Examiner, the present application provides explicit exemplification of modified peanut allergens and methods of preparing them. The application demonstrates that such modified peanut allergens have reduced IgE binding. Thus, the specification teaches that it is possible to modify a protein allergen to reduce IgE binding, provides successful evidence of such modification, and gives precise guidance for how to accomplish the modification. The present application claims, but does not contain an exemplification of, modified protein allergens that have been derived from other non-peanut allergens. The issue in the case is whether it would require undue experimentation to obtain these broader embodiments of the invention.

Appellant and the Examiner agree that *Wands* is the relevant precedent. The question, therefore, is whether the experimentation required to obtain the broader claimed modified allergens would be more burdensome or complex, or less likely to result in success, than the experimentation required in *Wands*. If not, the inventors are entitled to allowance of the disputed claims. The answer to this question is obtained by comparison of the experimental procedures in the two cases. We begin by summarizing *Wands*.

In re Wands

In *Wands*, the inventors developed a diagnostic for the Hepatitis B virus. In particular, the inventors identified a particular antibody that bound to a viral protein and could, therefore, be used to determine whether the virus was present. In *Wands*, the claims were broad enough to encompass both the particular antibodies described in the specification and other antibodies having the same or similar characteristics. The broadest claim encompassed any monoclonal, high affinity IgM antibody "having a binding affinity constant [...] of at least 10^9 M^{-1} ." The

specification described work by the inventors that led to the production of four antibodies falling within the scope of the claim. One hybridoma (a cell fusion that produces a single antibody) was deposited with the ATCC. Thus, the specification exemplified, at most, four antibodies that fell within the claim. The claim, however, encompassed all antibodies having the recited characteristics – a potentially infinite number of antibodies.

The Examiner rejected the Wands claim as too broad. He said that the disclosure in the specification was not commensurate in scope with the claim, that “the production of high Affinity IgM [...] antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.” *Id.* at 735.

The Federal Circuit reversed the Examiner (and the Board of Appeals). The Court held that the identification and production of other embodiments of the invention could have been achieved without undue experimentation. The Court said that “[a] patent need not disclose that which is well known in the art.” *Id.* at 735. The Court held that the generic claims should have been allowed because (1) the starting materials necessary to obtain the generically described (i.e., non-exemplified) antibodies were available to the public, (2) the methods used to generate antibodies and to screen them to determine which fall within the claims were well known in the art, and (3) useful antibodies could therefore be obtained without undue experimentation.

The case turned on the concept of undue experimentation. The Court said that a “considerable amount of experimentation is permissible, if it is merely routine.” *Id.* at 737. The Court then described the experimental procedure that would have been followed by scientists attempting to produce antibodies that were not expressly described in the *Wands* specification but that fell within the generic claims of the *Wands* application:

1. “The first step [...] is to immunize an animal.” (p. 737)
2. “Next the [mouse’s] spleen [...] is removed and the lymphocytes [in the spleen] are separated from the other spleen cells.” (p. 737)
3. “The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other, thus creating hybridomas.” (p. 737)
4. “Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures [of which] the first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells.” (p. 737)

5. “The next step [of the screening procedures] is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide.” (p. 737)

6. “After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen.” (pp. 737-738)

7. Antibodies that fall within the claims are selected by determination of their “numerical affinity constant, which must be measured using the [...] laborious Scotchard analysis.” (p. 738)

8. There is then performed “further screening to select those [antibodies] which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1} .” (p. 738)

The *Wands* inventors used these techniques. Some fusions were unsuccessful and produced no hybridomas; others produced hybridomas that made antibodies to the Hepatitis B surface antigen. Certain of these antibodies were screened. Some of the screened antibodies fell within the claims; others did not.

No undue experimentation in *Wands*

Despite the fact that a substantial amount of experimentation was required in *Wands* to obtain antibodies which were within the scope of the claims, the Court concluded that the experimentation was not “undue” and that the generic claims of the *Wands* patent were adequately enabled. The Court found that “there was a high level of skill in the art [...] and all of the methods needed to practice the invention were well-known.” *Id.* at 740. The Court also found that, although the technology involved screening hybridomas to determine which, if any, secreted antibodies with the desired characteristics, “[p]ractitioners of the art [were] prepared to screen negative hybridomas in order to find one that makes the desired antibody.” *Id.* at 740. The Court did not quantify the required likelihood of success, but noted that even a success rate as low as 2.8% would not necessarily require a conclusion of undue experimentation. *Id.* at 740.

This case is similar to *Wands*

As mentioned earlier, and as acknowledged by the Examiner, the present application provides explicit exemplification of modified peanut allergens that fall within the scope of claims. The present application clearly states that its teachings are also applicable to other non-peanut allergens (e.g., see pages 7-9). The present application clearly sets forth all the steps

necessary to identify and prepare suitable modified protein allergens that fall within the scope of the broadest claims, namely using patient sera to identify IgE binding epitopes; modifying a protein allergen sequence to alter identified IgE binding epitopes; and screening modified protein allergens to identify those with reduced binding. It is further undisputed that the sequences of numerous non-peanut protein allergens were known at the time of filing (a number of these are highlighted in the specification, e.g., see pages 7-9; others were known as evidenced by the numerous references and accession numbers that are provided in the "Official list of allergens," maintained by the IUIS Allergen Nomenclature Subcommittee and provided as **Attachment III**). For some of these protein allergens IgE binding sites were also already known (e.g., see page 8, lines 4-13). In addition, methods of identifying and modifying IgE binding sites were known and further described in the specification (e.g., see Examples 1 and 2). Those skilled in the art were also familiar with the methods that were used by the inventors to screen modified protein allergens for IgG and IgE binding and T-cell stimulation (e.g., see Examples 3 and 4).

At the time the application was filed, the starting materials necessary to obtain modified protein allergens were therefore available and the techniques for performing the necessary steps were well known and routine. Appellant respectfully submits that now that the inventors have demonstrated that the inventive methods *can* successfully be applied to protein allergens (i.e., that it is possible to generate modified protein allergens to which IgE binding is reduced but other characteristics remain unchanged), those skilled in the art would instantly realize that modified protein allergens derived from other allergens (1) would exist, (2) would operate in the same way to produce the same or similar results and (3) could be obtained using the techniques described in the application or which were well-known (indeed, routine) in the art.

There is no particular magic in the sequence of the peanut allergens Ara h 1, 2, and 3 that makes these protein allergens more susceptible to the inventive methods; the inventive principles, as discussed in the present application, apply to other protein allergens as well. In fact, quite the opposite might be expected. Peanut proteins are highly allergenic and, like many other food allergens (as distinguished, for example from most pollens and danders) present a significant risk of anaphylaxis to those allergic to them. The inventive demonstration that such anaphylactic proteins can be modified so that IgE binding is reduced as compared with the unmodified protein provides a strong teaching to those of ordinary skill in the art that other modified protein allergens with reduced IgE binding can also be made.

Others have prepared modified protein allergens according to the teachings of the application without undue experimentation

As further evidence that the claimed modified allergens may be obtained without undue experimentation, Appellant has identified a series of references showing that, after the present invention was made, people of ordinary skill in the art followed the steps taught in the present application (i.e., used patient sera to identify IgE binding epitopes, modified the protein sequence to alter identified IgE binding epitopes; and screened modified proteins to identify those with reduced binding) and were able to obtain, without undue experimentation, a variety of modified protein allergens that lie within the scope of the pending claims. More specifically, the following post-art references (already made of record in the Supplemental Response to Final Office Action that was filed September 19, 2002) were identified:

A. Timothy grass pollen allergen

Schramm et al., "Allergen engineering: variants of the Timothy grass pollen allergen Ph1 p 5b with reduced IgE-binding capacity but conserved T cell reactivity", *J. Immunol.*, 162:2406-2414, 1999.

B. English walnut allergen

Robotham et al., "Linear IgE epitope mapping of the English walnut (*Juglans regia*) major food allergen, Jug r 1", *J. Allergy Clin. Immunol.* 109:143-149, 2002.

C. Latex allergen

Beezhold et al., "Mutational analysis of the IgE epitopes in the latex allergen Hev b 5", *J. Allergy Clin. Immunol.* 107:1069-1076, 2001.

D. Ryegrass pollen allergen

Swoboda et al., "Mutants of the major ryegrass pollen allergen Lol p 5, with reduced IgE-binding capacity: candidates for grass pollen-specific immunotherapy", *Eur. J. Immunol.* 32:270-280, 2002.

E. Potato allergen

Astwood et al., "Identification and characterization of IgE binding epitopes of patatin, a major food allergen of potato", *J. Allergy Clin. Immunol.* 105:S184 (Abstract 555), 2000.

F. Soybean allergen

Helm et al., "Mutational analysis of the IgE-binding epitopes of P34/Gly m Bd 30K", *J. Allergy Clin. Immunol.* 105:378-384, 2000.

G. Shrimp allergen

Ayuso et al., "Identification and mutational analysis of major epitopes of the shrimp allergen Pen a 1 (Tropomyosin)", *J. Allergy Clin. Immunol.* 105:S140 (Abstract 423), 2000.

Lehrer et al., "Current understanding of food allergens", *Ann. N.Y. Acad. Sci.* 964:69-85, 2002.

Appellant respectfully submits that this evidence reinforces the fact that there is no particular magic in the sequence of peanut allergens that makes these allergens more susceptible to mutation; the inventive principles, once demonstrated may be readily applied to other protein allergens.

The Examiner's arguments fail to establish a case for lack of enablement

Appellant acknowledges the arguments that have been made by the Examiner (i.e., see heading # 4 in the Office Action mailed September 30, 2002). In particular, the Examiner cites various references that include a discussion of mutated peptides that failed to exhibit reduced IgE binding (Burks et al. and Stanley et al.) or T-cell stimulation (Fasler et al.) as compared to wild-type peptides. The Examiner suggests that these failures highlight the lack of predictability in the preparation of suitable modified protein allergens. However, the Examiner fails to recognize that even though the possibility exists that the initial modification of IgE binding epitopes may not identify suitable modified proteins, as was the case in *Wands* (and also in Burks et al., Stanley et al. and Fasler et al.), practitioners would be prepared to test more than one modification and to screen for useful modified proteins. The present case need only meet the enablement standard that was set in *Wands*. Appellant respectfully submits that the standard has been met, reconsideration and withdrawal of the rejection of claims 37-51, 53 and 60-71 for lack of enablement is therefore requested.

Claims 37-51, 53 and 60-71 are not Invalid for Lack of Written Description

Claims 37-51, 53 and 60-71 stand rejected for lack of written description (see heading # 5 in the Office Action mailed September 30, 2002). In supporting this rejection, the Examiner cites *University of California v. Eli Lilly and Co.* (119 F3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997)). This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). See also Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, “Written Description” Requirement, 66 Fed. Reg. 4, 1099 (2001).

Claim 37 (and claims 38-51, 53 and 65-71 that depend therefrom) recite a modified protein allergen whose amino acid sequence is:

- (1) substantially identical to that of an unmodified protein allergen except that
- (2) at least one amino acid has been modified in at least one IgE epitope so that
- (3) IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen.

Claims 60-62 further specify that the protein allergen is a food allergen. Claims 63-64 further specify that the protein allergen is a peanut allergen.

The Examiner has apparently taken the position that, the written description requirement is only satisfied for modified peanut allergens Ara h 1 (SEQ ID NO:2), Ara h 2 (SEQ ID NO:4) and Ara h 3 (SEQ ID NO:6) having mutations listed in Tables 4, 5 and 6, respectively. In particular, the Examiner appears to have taken the position that because no *sequence* of any non-peanut protein allergen (modified or otherwise) other than those listed above is *explicitly recited* in the specification, the specification does not describe any modified non-peanut protein allergen in such a way that one of ordinary skill in the art would have appreciated that the inventors had *possession* of it. Appellant respectfully submits that this position is untenable.

Appellant appreciates that certain court decisions, including *University of California v. Eli Lilly and Co.* have been interpreted to stand for the proposition that, in certain cases, nucleic acid or protein molecules cannot be properly described in a patent specification without explicit recitation of sequence information. However, this is not such a case. It is important to note that a determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art *at the time that the invention was filed* (*In re Alton*, 76 F3d 1168, 37 USPQ 2d 1578 (Fed. Cir. 1996)). In *University of California v. Eli Lilly and Co.*, the patent applications in issue were filed in 1977 and 1979. These applications therefore predated the molecular biology revolution, during which reliable

strategies for determining nucleic acid sequences, altering them by site directed mutagenesis, and amplifying the generated nucleic acid became routine. As a result of these developments, workers of ordinary skill require much less *explicit* sequence information to establish possession of a given nucleic acid or protein. The present application was filed on January 6, 2000; its earliest priority date is in 1996, more than fifteen years *after* the latest application at issue in *University of California v. Eli Lilly and Co.* and almost twenty years after the earliest. The intervening developments in nucleic acid characterization and manipulation were part of the common knowledge of a person of ordinary skill in the at the time the present application was filed. In the context of such knowledge, the present application provides more than enough description of modified protein allergens to demonstrate that the inventors were in possession of the full scope of the claimed invention.

For example, the specification itself clearly states that its teachings are applicable to other unmodified protein allergens, e.g., protein allergens from foods, insects, molds, dusts, grasses, trees, weeds, mammals, etc. Moreover, the specification also provides written description of:

(1) references that list known amino acid sequences and IgE epitopes for a wide variety of unmodified protein allergens, e.g., allergens from cow milk, egg, codfish, hazel nut, soybean, and shrimp (see pages 7-9);

(2) identification of IgE binding sites in a selected protein allergen, if they are unknown (see pages 9-11), coupled with a demonstration that the described strategies are successful when applied to peanut allergens (see Example 1);

(3) disruption of identified IgE epitopes, coupled with a demonstration that the described strategies are successful when applied to peanut allergens (see Examples 2 and 3).

The present specification and claims as originally filed therefore clearly put the public on notice that the inventors considered the present claims to be within the scope of their invention. Furthermore, as Appellant has previously discussed, those skilled in the art would have fully appreciated and understood the provided description as properly defining the invention. They would have appreciated that modified protein allergens derived from other allergens (1) would exist, (2) would operate in the same way to produce the same or similar results and (3) could be obtained using techniques which were well-known in the art. The teachings of the present application therefore provide more than adequate written description to support the present claims. The rejection for lack of written description should be removed.

Claims 65-69 are not Invalid for Containing New Matter

The Examiner has questioned the support for the recitation in claims 65-69 of a modified protein allergen that comprises at least one IgE epitope with 1-6, 1-5, 1-4, 1-3 or 1-2 modified amino acid residues (see heading # 6 in the Office Action mailed September 30, 2002). Appellant respectfully submits that these claims are fully supported by the specification and claims as originally filed. In particular, original claim 14 reads “a modified allergen [...] comprising at least one IgE binding site [...] modified by *at least one* amino acid change [...].” Original claim 14 therefore makes it perfectly clear that the present invention encompasses modified protein allergens with at least one IgE binding site that includes *more than one* modified amino acid residue. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively). The specification and claims as originally filed therefore clearly support the language of pending claims 65-69.

Claims 37, 60 and 63 are not Indefinite for Reciting the Term “Substantially”

The Examiner has taken the position that claims 37, 60 and 63 are indefinite under 35 U.S.C. § 112, second paragraph for reciting the term “substantially” without providing a definition of the term in the specification (see heading # 8 in the Office Action mailed September 30, 2002). Appellant respectfully disagrees. The courts have clearly stated that expressions such as “substantially” may be used in patent claims when warranted by the nature of invention, in order to accommodate the minor variations that may be appropriate to secure the invention. *Verve LLC v. Crane Cams*, 311 F.3d 1116 (Fed. Cir. 2002). The nature of the presently claimed invention is such that minor variations from an otherwise “identical amino acid sequence” (e.g., the addition of a single terminal methionine during recombinant synthesis) could be made without losing the benefit of the present invention. One skilled in the art, upon reading the present specification, would readily recognize such trivial variations. No more is required. In fact, as noted in Judge Hand’s opinion in *Musher Foundation v. Alba Trading Co.*, 326 U.S. 770 (1945):

‘Substantially’ is not of itself fatal to a claim [...] indeed, it must always be implied in every claim, even when not introduced, and adds nothing when it is. Were this not true, few patents could be given any protection, for some departures from the precise disclosure are nearly always possible without losing the benefit of the invention.

For all of these reasons, withdrawal of the rejection is earnestly requested.

Claims 37-39, 41-46, 48-51 and 53 are not anticipated by U.S. Pat. No. 5,547,669

The Examiner has rejected claims 37-39, 41-46, 48-51 and 53 under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat. No. 5,547,669. This rejection is respectfully traversed. As discussed in the Response to Office Action filed June 18, 2002, the “recombitope peptides” that are taught by U.S. Pat. No. 5,547,669 cannot anticipate these claims since they do not satisfy the limitations of every claimed element. In particular, one skilled in the art would immediately recognize that a “recombitope peptide” does not have an amino acid sequence that is “substantially identical to that of an unmodified allergen except that at least one amino acid has been modified in at least one IgE epitope.”

In general, “recombitope peptides” are peptides that include at least two T-cell epitopes derived from the same or from different protein antigens (e.g., see Abstract). It is presumably undisputed that a “recombitope peptide” that includes T-cell epitopes derived from *different* protein antigens will necessarily have an amino acid sequence that bears no resemblance whatsoever to the amino acid sequence of either parent antigen. Further, when the T-cell epitopes are from the *same* protein antigen we are taught that these should be arranged in a *noncontiguous configuration*, namely:

“an arrangement of amino acids comprising T-cell epitopes [...] which is *different* than that of an amino acid sequence present in the protein allergen or other protein antigen from which the epitopes [...] are derived.” (see lines 3-8, column 7, emphasis added).

and a *nonsequential* order, namely:

“an order *different* from the order of the amino acids of the native protein allergen or other protein antigen from which the T-cell epitopes [...] are derived [...]” (e.g., see lines 8-14, column 7, emphasis added).

In order to reduce the likelihood of IgE binding, IgE epitopes are preferably *excluded* from the amino acid sequences of “recombitope peptides”:

“Those peptide regions found to bind immunoglobulin E and cause the release of mediators from mast cell or basophils in greater than approximately 10-15% of the allergic sera tested are *preferably not included* in the peptide regions arranged to form recombitope peptides”. (e.g., see lines 5-9, column 8, emphasis added)

Again it is presumably undisputed that these “recombitope peptides” will also have an amino acid sequence that bears no resemblance to the amino acid sequence of the parent antigen.

As the foregoing sections highlight, U.S. Pat. No. 5,547,669 teaches methods that involve extracting, rearranging and pasting T-cell epitopes that were originally present in one or more natural protein antigens. IgE epitopes are preferably extracted and removed entirely. The resultant "recombitope peptides" are wholly artificial peptides that bear no resemblance whatsoever to their parent antigen(s). U.S. Pat. No. 5,547,669 therefore teaches strongly *away* from modified protein allergens whose amino acid sequence is substantially *identical* to that of an unmodified protein allergen *except that* at least one amino acid has been modified in at least one IgE epitope of the unmodified protein allergen, as recited in the present claims. The substitutions, deletions, or additions that are referred to by the Examiner (e.g., lines 1-5, 15-17 and 59-62, column 15) do not remedy these deficiencies, if anything they further differentiate "recombitope peptides" from the claimed invention. U.S. Pat. No. 5,547,669 does anticipate or render obvious claims 37-39, 41-46, 48-51 and 53. Withdrawal of the rejection is earnestly requested.

Claims 37, 60-61 and 63-71 are not anticipated by Burks et al. (1997)

The Examiner has rejected claims 37, 60-61 and 63-71 under 35 U.S.C. § 102(a) as being anticipated by Burks et al. (*Eur. J. Biochem.* 245:334-339, 1997). Appellant respectfully disagrees and notes that the teachings of Burks et al. (1997) were included near *verbatim* in U.S. Serial No. 08/717,933 and PCT/US96/15222 both filed September 23, 1996 (see pp. 133-155 and the Figures referred to therein). The present application properly claims priority to these 1996 filings. Burks et al. (1997) was published after this priority date and cannot therefore be used as prior art under 35 U.S.C. § 102(a). Withdrawal of the rejection is earnestly requested.

Claims 37 and 47 are not obvious in light of U.S. Pat. No. 5,547,669 and Hoyne et al.

The Examiner has rejected claims 37 and 47 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 5,547,669 in view of Hoyne et al. (*Immunology and Cell Biology* 74:180-186, 1996). The teachings of U.S. Pat. No. 5,547,669 and its deficiencies with regards to independent claim 37 have been discussed *supra*. Hoyne et al. is cited solely as teaching certain elements added in dependent claim 47, specifically certain adjuvants. The Examiner indicates no teaching or suggestion in Hoyne et al. that could overcome the deficiencies of U.S. Pat. No. 5,547,669. Withdrawal of the rejection is earnestly requested.

Claim 37 is not obvious in light of U.S. Pat. No. 5,547,669 and Burks et al. (1994)

The Examiner has rejected claim 37 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 5,547,669 in view of Burks et al. (*J. Allergy Clin. Immunol.* 93:743-750, 1994). The teachings of U.S. Pat. No. 5,547,669 and its deficiencies with regards to claim 37 have been discussed *supra*. Burks et al. (1994) is a secondary reference that is cited solely as teaching unmodified protein allergens, namely peanut Ara h 1 and Ara h 2, and alleged IgE epitopes of these. For the record, Appellant notes that Burks et al. (1994) does not teach IgE epitopes of Ara h 2 and only identifies the existence of three IgE epitopes of Ara h 1 based on an ELISA inhibition assay using monoclonal antibodies – the locations of these three IgE epitopes within the Ara h 1 amino acid sequence are not provided. Besides, even if Burks et al. (1994) had taught the location of any IgE epitope of Ara h 1 and/or Ara h 2, the Examiner has failed to point to any teaching or suggestion in Burks et al. (1994) that could overcome the aforementioned deficiencies of U.S. Pat. No. 5,547,669. Withdrawal of the rejection is earnestly requested.

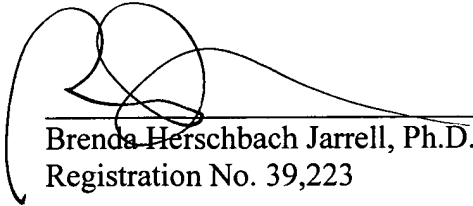
Claims 60-62 are not obvious in light of U.S. Pat. No. 5,547,669 or Burks et al. (1997) each in combination with U.S. Pat. No. 5,449,669

The Examiner has rejected claims 60-62 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 5,547,669 or Burks et al. (1997) each in view of U.S. Pat. No. 5,449,669. The teachings of U.S. Pat. No. 5,547,669 and its lackings have been discussed *supra*. As discussed *supra*, Burks et al. (1997) is not available as prior art under 35 U.S.C. § 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. No. 5,449,669 that could overcome the deficiencies of U.S. Pat. No. 5,547,669. Withdrawal of the rejection is earnestly requested.

Conclusion

Appellant again concludes with the belief that claims 37-51, 53 and 60-71 as amended by the Amendment filed herewith are fully supported by the specification as filed and allowable over the art of record. Allowance of these claims is earnestly requested.

Respectfully submitted,



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Dated: June 12, 2003

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Attachment I

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending before Entrance of Amendment

Claims Pending before Entry of Amendment

37. **(Previously amended)** A modified protein allergen whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen.
38. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified protein allergen.
39. **(Previously amended)** The modified protein allergen of claim 37 wherein the at least one IgE epitope is one that is recognized when the unmodified protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the unmodified protein allergen.
40. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one modified amino acid is located in the center of the at least one IgE epitope.
41. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been modified by substitution.
42. **(Previously amended)** The modified protein allergen of claim 41 wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid.

43. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to activate T cells.
44. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to bind IgG.
45. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to initiate a Th1-type response.
46. **(Previously amended)** The modified protein allergen of claim 37 wherein the modified protein allergen is a portion of the unmodified protein allergen.
47. **(Previously amended)** A composition comprising the modified protein allergen of claim 37 and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFN γ , and immune stimulatory sequences.
48. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen is made in a transgenic plant or animal.
49. **(Previously added)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of plants and animals.
50. **(Previously added)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells.
51. **(Previously amended)** The modified protein allergen of claim 37 wherein the unmodified protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes.

52. **(Previously added)** The modified protein allergen of claim 37 wherein the natural protein allergen is a peanut protein selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.
53. **(Previously amended)** The modified protein allergen of claim 37 made by the process of:
- identifying at least one IgE epitope in an unmodified protein allergen;
 - preparing at least one modified protein allergen whose amino acid sequence is substantially identical to that of the unmodified protein allergen except, that at least one amino acid has been modified in the at least one IgE epitope;
 - screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified protein allergen; and
 - selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified protein allergen.
54. **(Previously added)** In combination, a natural protein allergen and a masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen in such a way that IgE binding is reduced as compared with IgE binding to the natural protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen.
55. **(Previously added)** The combination of claim 54 wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen.
56. **(Previously added)** The combination of claim 54 wherein the masking compound is an antibody that binds non-covalently to the at least one IgE epitope.

57. **(Previously added)** The combination of claim 54 wherein the combination retains the ability to activate T cells.
58. **(Previously added)** The combination of claim 54 wherein the combination retains the ability to bind IgG.
59. **(Previously added)** The combination of claim 54 wherein the combination retains the ability to initiate a Th1-type response.
60. **(Previously added)** A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen.
61. **(Previously added)** The modified protein allergen of claim 60 wherein the unmodified food allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.
62. **(Previously added)** The modified protein allergen of claim 61 wherein the unmodified food allergen is obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.
63. **(Previously added)** A modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified peanut allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the

unmodified peanut allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut allergen.

64. **(Previously added)** The modified peanut allergen of claim 63 wherein the unmodified peanut allergen is selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.
65. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-6 amino acid residues that are modified as compared with the unmodified allergen.
66. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-5 amino acid residues that are modified as compared with the unmodified allergen.
67. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-4 amino acid residues that are modified as compared with the unmodified allergen.
68. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-3 amino acid residues that are modified as compared with the unmodified allergen.
69. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-2 amino acid residues that are modified as compared with the unmodified allergen.
70. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1 amino acid residue that is modified as compared with the unmodified allergen.

71. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen.

Attachment II

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending after Entrance of Amendment

Claims Pending after Entrance of Amendment

37. **(Previously amended)** A modified protein allergen whose amino acid sequence is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen.
38. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified protein allergen.
39. **(Previously amended)** The modified protein allergen of claim 37 wherein the at least one IgE epitope is one that is recognized when the unmodified protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the unmodified protein allergen.
40. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one modified amino acid is located in the center of the at least one IgE epitope.
41. **(Previously amended)** The modified protein allergen of claim 37 wherein at least one amino acid in the at least one IgE epitope of the unmodified protein allergen has been modified by substitution.
42. **(Previously amended)** The modified protein allergen of claim 41 wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid.
43. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to activate T cells.

44. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to bind IgG.
45. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen retains the ability to initiate a Th1-type response.
46. **(Previously amended)** The modified protein allergen of claim 37 wherein the modified protein allergen is a portion of the unmodified protein allergen.
47. **(Previously amended)** A composition comprising the modified protein allergen of claim 37 and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFN γ , and immune stimulatory sequences.
48. **(Previously added)** The modified protein allergen of claim 37 wherein the modified protein allergen is made in a transgenic plant or animal.
49. **(Previously added)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of plants and animals.
50. **(Previously added)** The modified protein allergen of claim 37 expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells.
51. **(Previously amended)** The modified protein allergen of claim 37 wherein the unmodified protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes.
52. **(Canceled)**

53. **(Previously amended)** The modified protein allergen of claim 37 made by the process of:

identifying at least one IgE epitope in an unmodified protein allergen;
preparing at least one modified protein allergen whose amino acid sequence is substantially identical to that of the unmodified protein allergen except, that at least one amino acid has been modified in the at least one IgE epitope;
screening for IgE binding to the at least one modified protein allergens by contacting the at least one modified protein allergens with serum IgE taken from at least one individual that is allergic to the unmodified protein allergen; and
selecting a modified protein allergen with decreased binding to IgE as compared to the unmodified protein allergen.

- 54-59. **(Canceled)**

60. **(Previously added)** A modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified food allergen is contacted with serum IgE from an individual that is allergic to the unmodified food allergen.
61. **(Currently amended)** The modified food allergen of claim 60 wherein the unmodified food allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.
62. **(Currently amended)** The modified food allergen of claim 61 wherein the unmodified food allergen is obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.

63. **(Previously added)** A modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified peanut allergen is reduced as compared with IgE binding to the unmodified food allergen, the at least one IgE epitope being one that is recognized when the unmodified peanut allergen is contacted with serum IgE from an individual that is allergic to the unmodified peanut allergen.
64. **(Previously added)** The modified peanut allergen of claim 63 wherein the unmodified peanut allergen is selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.
65. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-6 amino acid residues that are modified as compared with the unmodified allergen.
66. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-5 amino acid residues that are modified as compared with the unmodified allergen.
67. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-4 amino acid residues that are modified as compared with the unmodified allergen.
68. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-3 amino acid residues that are modified as compared with the unmodified allergen.
69. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1-2 amino acid residues that are modified as compared with the unmodified allergen.

70. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein the at least one IgE epitope contains 1 amino acid residue that is modified as compared with the unmodified allergen.
71. **(Previously added)** The modified allergen of claim 37, claim 60, or claim 63, wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen.

Attachment III

to

Appeal Brief under 37 C.F.R. § 1.192

“Official list of allergens” maintained by the IUIS Allergen Nomenclature Subcommittee
printed on June 8, 2003 from <ftp://biobase.dk/pub/who-iuis/allergen.list>

Official list of allergens
 IUIS Allergen Nomenclature Subcommittee
<ftp://biobase.dk/pub/who-iuis/allergen.list>

2000.03.01 Jorgen Nedergaard Larsen and Henning Lowenstein,
 ALK-Abello, Boge Alle 6-8, DK-2970 Horsholm, Denmark
 Please report changes, additions or comments to jnlarsen@inet.uni2.dk

Legends: MW determined by reducing SDS-PAGE; asterisk: MW deduced from sequence;
 C: cDNA seq; P: peptide seq;

Allergen source	Systematic and original names	MW kDa	sequence data	Accession # or References

A. Weed pollens				
Asterales				
Ambrosia artemisiifolia				
(short ragweed)	Amb a 1; antigen E	38	C	8,20
	Amb a 2; antigen K	38	C	8,21
	Amb a 3; Ra3	11	C	22
	Amb a 5; Ra5	5	C	11,23
	Amb a 6; Ra6	10	C	24,25
	Amb a 7; Ra7	12	P	26
	Amb a ?	11	C	27
Ambrosia trifida				
(giant ragweed)	Amb t 5; Ra5G	4.4	C	9,10,28
Artemisia vulgaris				
(mugwort)	Art v 1;	27-29	C	28A
	Art v 2;	35	P	29
Helianthus annuus				
(sunflower)	Hel a 1;	34	-	29a
	Hel a 2; profilin	15.7	C	Y15210
Mercurialis annua				
	Mer a 1; profilin	14-15	C	Y13271
B. Grass pollens				
Poales				
Cynodon dactylon				
(Bermuda grass)	Cyn d 1;	32	C	30,S83343
	Cyn d 7;		C	31,X91256
	Cyn d 12; profilin	14	C	31a,Y08390
Dactylis glomerata				
(orchard grass)	Dac g 1; AgDg1	32	P	32
	Dac g 2;	11	C	33,S45354
	Dac g 3;		C	33a,U25343
	Dac g 5;	31	P	34
Holcus lanatus				
(velvet grass)	Hol l 1;		C	Z27084,Z68893

Lolium perenne (rye grass)	Lol p 1; group I	27	C	35, 36
	Lol p 2; group II	11	C	37, 37a, X73363
	Lol p 3; group III	11	C	38
	Lol p 5; Lol p IX, Lol p Ib	31/35	C	34, 39
	Lol p 11; trypsin inh. Related	16		39a
Phalaris aquatica (canary grass)	Pha a 1;		C	40, S80654
Phleum pratense (timothy)	Phl p 1;	27	C	X78813
	Phl p 2;		C	41, X75925
	Phl p 4;		P	41A
	Phl p 5; Ag25	32	C	42
	Phl p 6;		C	43, Z27082
	Phl p 12; profilin		C	44, X77583
	Phl p 13; polygalacturonase	55-60	C	AJ238848
Poa pratensis (Kentucky blue grass)	Poa p 1; group I	33	P	46
	Poa p 5;	31/34	C	34, 47
Sorghum halepense (Johnson grass)	Sor h 1;		C	48
C. Tree pollens				
Fagales:				
Alnus glutinosa (alder)	Aln g 1;	17	C	S50892
Betula verrucosa (birch)	Bet v 1;	17	C	see iso-list
	Bet v 2; profilin	15	C	M65179
	Bet v 3;		C	X79267
	Bet v 4;	8	C	X87153/S54819
	Bet v 6; isoflavone reductase homologue	33.5	C	AF135127
	Bet v 7; cyclophilin	18	P	P81531
Carpinus betulus (hornbeam)	Car b 1;	17	C	see iso-list
Castanea sativa (chestnut)	Cas s 1; Bet v 1 homologue	22	P	52
	Cas s 5; chitinase			
Corylus avellana (hazel)	Cor a 1;	17	C	see iso-list
Quercus alba (white oak)	Que a 1;	17	P	54

Lamiales:

Oleaceae:				
Fraxinus excelsior (ash)	Fra e 1;	20	P	58A
Ligustrum vulgare (privet)	Lig v 1;	20	P	58A
Olea europea (olive)	Ole e 1;	16	C	59, 60
	Ole e 2; profilin	15-18	C	60A
	Ole e 3;	9.2		60B
	Ole e 4;	32	P	P80741
	Ole e 5; superoxide dismutase	16	P	P80740
	Ole e 6;	10	C	U86342
	Ole e 7;	?	P	P81430
Syringa vulgaris (lilac)	Syr v 1;	20	P	58A
Plantaginaceae:				
Plantago lanceolata (English plantain)	Pla l 1;	18	P	P842242
Pinales:				
Cryptomeria japonica (sugi)	Cry j 1;	41-45	C	55, 56
	Cry j 2;		C	57, D29772
Cupressus arizonica (cypress)	Cup a 1;	43	C	A1243570
Juniperus ashei (mountain cedar)	Jun a 1;	43	P	P81294
	Jun a 3;	30	P	P81295
Juniperus oxycedrus (prickly juniper)	Jun o 2; calmodulin-like	29	C	AF031471
Juniperus sabinoides (mountain cedar)	Jun s 1;	50	P	58
Juniperus virginiana (eastern red cedar)	Jun v 1;	43	P	P81825
D. Mites				
Acarus siro (mite)	Aca s 13; fatty acid-bind.prot.14*		C	AJ006774
Blomia tropicalis (mite)	Blo t 5;		C	U59102
	Blo t 12; Bt11a		C	U27479
	Blo t 13; Bt6 fatty acid-binding prot.		C	U58106

Dermatophagoides pteronyssinus				
(mite)	Der p 1; antigen P1	25	C	61
	Der p 2;	14	C	62
	Der p 3; trypsin	28/30	C	63
	Der p 4; amylase	60	P	64
	Der p 5;	14	C	65
	Der p 6; chymotrypsin	25	P	66
	Der p 7;	22-28	C	67
	Der p 8; glutathione transferase		C	67A
	Der p 9; collagenolytic serine prot.		P	67B
	Der p 10; tropomyosin	36	C	Y14906
	Der p 14; apolipophorin like p.		C	Epton p.c.
Dermatophagoides microceras				
(mite)	Der m 1;	25	P	68
Dermatophagoides farinae				
(mite)	Der f 1 ;	25	C	69
	Der f 2 ;	14	C	70, 71
	Der f 3 ;	30	C	63
	Der f 10; tropomyosin		C	72
	Der f 11; paramyosin	98	C	72a
	Der f 14; Mag3, apolipophorin		C	D17686
Euroglyphus maynei				
(mite)	Eur m 14; apolipophorin	177	C	AF149827
Lepidoglyphus destructor				
(storage mite)	Lep d 2.0101;	15	C	73, 74, 75
	Lep d 2.0102;	15	C	75
E. Animals				
Bos domesticus				
(domestic cattle)	Bos d 2; Ag3, lipocalin	20	C	76, L42867
(see also foods)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77
	Bos d 8; caseins	20-30		77
Canis familiaris				
(Canis domesticus)	Can f 1;	25	C	78, 79
(dog)	Can f 2;	27	C	78, 79
	Can f ?; albumin		C	S72946
Equus caballus				
(domestic horse)	Equ c 1; lipocalin	25	C	U70823
	Equ c 2; lipocalin	18.5	P	79A, 79B
Felis domesticus				
(cat saliva)	Fel d 1; cat-1	38	C	15
Mus musculus				
(mouse urine)	Mus m 1; MUP	19	C	80, 81

Rattus norvegicus
(rat urine)

Rat n 1

17

C

82,83

F. Fungi

1. Ascomycota

1.1 Dothidiales

Alternaria alternata

Alt a 1;	28	C	U82633
Alt a 2;	25	C	
Alt a 3; heat shock prot. 70		C	U87807, U87808
Alt a 4; prot.disulfidisomerase	57	C	X84217
Alt a 6; acid.ribosomal prot P2	11	C	X78222, U87806
Alt a 7; YCP4 protein	22	C	X78225
Alt a 10; aldehyde dehydrogen.	53	C	X78227, P42041
Alt a 11; enolase	45	C	U82437
Alt a 12;acid.ribosomal prot P1	11	C	X84216

Cladosporium herbarum

Cla h 1;	13		83a, 83b
Cla h 2;	23		83a, 83b
Cla h 3; aldehyde dehydrogenase	53	C	X78228
Cla h 4; acid.ribosomal prot P2	11	C	X78223
Cla h 5; YCP4 protein	22	C	X78224
Cla h 6; enolase	46	C	X78226
Cla h 12;acid.ribosomal prot P1	11	C	X85180

1.2 Eurotiales

Aspergillus flavus

Asp fl 13; alkaline serine proteinase	34		84
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Aspergillus fumigatus

Asp f 1;	18	C	M83781, S39330
Asp f 2;	37	C	U56938
Asp f 3; peroxisomal protein	19	C	U20722
Asp f 4;	30	C	AJ001732
Asp f 5; metalloprotease	42	C	Z30424
Asp f 6; Mn superoxide dismutase	26.5	C	U53561
Asp f 7;	12	C	AJ223315
Asp f 8; ribosomal protein P2	11	C	AJ224333
Asp f 9;	34	C	AJ223327
Asp f 10; aspartic protease	34	C	X85092
Asp f 11; peptidyl-prolyl isom	24		84a
Asp f 12; heat shock prot. P90	90	C	85
Asp f 13; alkaline serine proteinase	34		84b
Asp f 15;	16	C	AJ002026
Asp f 16;	43	C	g3643813
Asp f 17;		C	AJ224865
Asp f 18; vacuolar serine proteinase	34		84c

<i>Aspergillus niger</i>				
	Asp n 14; beta-xylosidase	105	C	AF108944
	Asp n 18; vacuolar serine			
	proteinase	34	C	84b
	Asp n ?;	85	C	Z84377
<i>Aspergillus oryzae</i>				
	Asp o 13; alkaline serine			
	proteinase	34	C	X17561
	Asp o 21; TAKA- α -amylase A	53	C	D00434, M33218
<i>Penicillium brevicompactum</i>				
	Pen b 13; alkaline serine			
	Proteinase	33		86a
<i>Penicillium citrinum</i>				
	Pen c 3; peroxisomal membrane			
	protein	18		86b
	Pen c 13; alkaline serine			
	proteinase	33		86a
	Pen c 19; heat shock prot. P70	70	C	U64207
<i>Penicillium notatum</i>				
	Pen n 13; alkaline serine			
	proteinase	34		89
	Pen n 18; vacuolar serine			
	proteinase	32		89
	Pen n 20; N-acetyl			
	glucosaminidase	68		87
<i>Penicillium oxalicum</i>				
	Pen o 18; vacuolar serine			
	proteinase	34		89
1.3 Onygenales				
<i>Trichophyton rubrum</i>				
	Tri r 2;		C	90
	Tri r 4; serine protease		C	90
<i>Trichophyton tonsurans</i>				
	Tri t 1;	30	P	91
	Tri t 4; serine protease	83	C	90
1.4 Saccharomycetales				
<i>Candida albicans</i>				
	Cand a 1;	40	C	88
<i>Candida boidinii</i>				
	Cand b 2;	20	C	J04984, J04985
2 Basidiomycota				
2.1 Basidiolelastomycetes				
<i>Malassezia furfur</i>				
	Mala f 1;			91a

Mala f 2; MF1	21	C	AB011804
peroxisomal membrane protein			
Mala f 3; MF2	20	C	AB011805
peroxisomal membrane protein			
Mala f 4;	35	C	Takesako, p.c.
Mala f 5;	18*	C	AJ011955
Mala f 6; cyclophilin homologue	17*	C	AJ011956

2.2 Basidiomycetes

Psilocybe cubensis

Psi c 1;			
Psi c 2; cyclophilin	16		91b

Coprinus comatus (shaggy cap)

Cop c 1; leucine zipper prot.	11	C	AJ132235
Cop c 2;			Brander, p.c.
Cop c 3;			Brander, p.c.
Cop c 5;			Brander, p.c.
Cop c 7;			Brander, p.c.

G. Insects

Aedes aegyptii (mosquito)

Aed a 1; apyrase	68	C	L12389
Aed a 2;	37	C	M33157

Apis mellifera (honey bee)

Api m 1; phospholipase A2	16	C	92
Api m 2; hyaluronidase	44	C	93
Api m 4; melittin	3	C	94
Api m 6;	7-8	P	Kettner, p.c.

Bombus pennsylvanicus (bumble bee)

Bom p 1; phospholipase	16	P	95
Bom p 4; protease		P	95

Blattella germanica (German cockroach)

Bla g 1; Bd90k		C	
Bla g 2; aspartic protease	36	C	96
Bla g 4; calycin	21	C	97
Bla g 5; glutathione transf.	22	C	98
Bla g 6; troponin C	27	C	98

Periplaneta americana (American cockroach)

Per a 1; Cr-P11		C	
Per a 3; Cr-P1	72-78	C	98A
Per a 7; tropomyosin	37	C	Y14854

Chironomus thummi thummi (midges)

Chi t 1-9; hemoglobin	16	C	99
Chi t 1.01; component III	16	C	P02229
Chi t 1.02; component IV	16	C	P02230
Chi t 2.0101; component I	16	C	P02221
Chi t 2.0102; component IA	16	C	P02221
Chi t 3; component II-beta	16	C	P02222
Chi t 4; component IIIA	16	C	P02231

	Chi t 5; component VI	16	C	P02224
	Chi t 6.01; component VIIA	16	C	P02226
	Chi t 6.02; component IX	16	C	P02223
	Chi t 7; component VIIB	16	C	P02225
	Chi t 8; component VIII	16	C	P02227
	Chi t 9; component X	16	C	P02228
<i>Dolichovespula maculata</i>				
(white face hornet)	Dol m 1; phospholipase A1	35	C	100
	Dol m 2; hyaluronidase	44	C	101
	Dol m 5; antigen 5	23	C	102,103
<i>Dolichovespula arenaria</i>				
(yellow hornet)	Dol a 5; antigen 5	23	C	104
<i>Polistes annularies</i>				
(wasp)	Pol a 1; phospholipase A1	35	P	105
	Pol a 2; hyaluronidase	44	P	105
	Pol a 5; antigen 5	23	C	104
<i>Polistes dominulus</i>				
(Mediterranean paper wasp)	Pol d 1;			DR Hoffman
	Pol d 4; serine protease	32-34	C	DR Hoffman
	Pol d 5;			P81656
<i>Polistes exclamans</i>				
(wasp)	Pol e 1; phospholipase A1	34	P	107
	Pol e 5; antigen 5	23	C	104
<i>Polistes fuscatus</i>				
(wasp)	Pol f 5; antigen 5	23	C	106
<i>Polistes metricus</i>				
(wasp)	Pol m 5; antigen 5	23	P	106
<i>Vespa crabo</i>				
(European hornet)	Vesp c 1; phospholipase	34	P	107
	Vesp c 5.0101; antigen 5	23	C	106
	Vesp c 5.0102; antigen 5	23	C	106
<i>Vespa mandarina</i>				
(giant asian hornet)	Vesp m 1.01;			DR Hoffman
	Vesp m 1.02;			DR Hoffman
	Vesp m 5;			P81657
<i>Vespula flavopilosa</i>				
(yellowjacket)	Ves f 5; antigen 5	23	C	106
<i>Vespula germanica</i>				
(yellowjacket)	Ves g 5; antigen 5	23	C	106
<i>Vespula maculifrons</i>				
(yellowjacket)	Ves m 1; phospholipase A1	33.5	C	108
	Ves m 2; hyaluronidase	44	P	109
	Ves m 5; antigen 5	23	C	104

<i>Vespula pennsylvanica</i> (yellowjacket)	Ves p 5; antigen 5	23	C	106
<i>Vespula squamosa</i> (yellowjacket)	Ves s 5; antigen 5	23	C	106
<i>Vespula vidua</i> (wasp)	Ves vi 5;	23	C	106
<i>Vespula vulgaris</i> (yellowjacket)	Ves v 1; phospholipase A1	35	C	105A
	Ves v 2; hyaluronidase	44	P	105A
	Ves v 5; antigen 5	23	C	104
<i>Myrmecia pilosula</i> (Australian jumper ant)	Myr p 1;		C	X70256
	Myr p 2;		C	S81785
<i>Solenopsis geminata</i> (tropical fire ant)	Sol g 2;			DR Hoffman
	Sol g 4;			DR Hoffman
<i>Solenopsis invicta</i> (fire ant)	Sol i 2;	13	C	110,111
	Sol i 3;	24	C	110
	Sol i 4;	13	C	110
<i>Solenopsis saevissima</i> (brazilian fire ant)	Sol s 2;			DR Hoffman
H. Foods				
<i>Gadus callarias</i> (cod)	Gad c 1; allergen M	12	C	112,113
<i>Salmo salar</i> (Atlantic salmon)	Sal s 1; parvalbumin	12	C	X97824 X97825
<i>Bos domesticus</i> (domestic cattle) (milk) (see also animals)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77
	Bos d 8; caseins	20-30		77
<i>Gallus domesticus</i> (chicken)	Gal d 1; ovomucoid	28	C	114,115
	Gal d 2; ovalbumin	44	C	114,115
	Gal d 3; conalbumin (Ag22)	78	C	114,115
	Gal d 4; lysozyme	14	C	114,115
	Gal d 5; serum albumin	69	C	X60688
<i>Metapenaeus ensis</i> (shrimp)	Met e 1; tropomyosin		C	U08008
<i>Penaeus aztecus</i> (shrimp)	Pen a 1; tropomyosin	36	P	116

Penaeus indicus (shrimp)	Pen i 1; tropomyosin	34	C	117
Todarodes pacificus (squid)	Tod p 1; tropomyosin	38	P	117A
Haliotis Midae (abalone)	Hal m 1	49	-	117B
Apium graveolens (celery)	Api g 1; Bet v 1 homologue Api g 4; profilin Api g 5;	16* 55/58	C P	Z48967 AF129423 P81943
Brassica juncea (oriental mustard)	Bra j 1; 2S albumin	14	C	118
Brassica rapa (turnip)	Bra r 2; prohevein-like protein	25	?	P81729
Hordeum vulgare (barley)	Hor v 15; BMAI-1	15	C	119
Zea mays (maize, corn)	Zea m 14; lipid transfer prot.	9	P	P19656
Oryza sativa (rice)	Ory s 1;		C	U31771
Corylus avellana (hazelnut)	Cor a 1.0401; Bet v 1 homologue	17	C	AF136945
Malus domestica (apple)	Mal d 1; Bet v 1 homologue Mal d 2; thaumatin homologue Mal d 3; lipid transfer protein	9	C C C	X83672 AJ243427 Pastorello
Pyrus communis (pear)	Pyr c 1; Bet v 1 homologue Pyr c 4; profilin Pyr c 5; isoflavone reductase homologue	18 14 33.5	C C C	AF05730 AF129424 AF071477
Persea americana (avocado)	Pers a 1; endochitinase	32	C	Z78202
Prunus armeniaca (apricot)	Pru ar 1; Bet v 1 homologue Pru ar 3; lipid transfer protein	9	C P	U93165
Prunus avium (sweet cherry)	Pru av 1; Bet v 1 homologue Pru av 2; thaumatin homologue Pru av 4; profilin	15	C C C	U66076 U32440 AF129425
Prunus persica (peach)	Pru p 3; lipid transfer protein	10	P	P81402

Sinapis alba (yellow mustard)	Sin a 1; 2S albumin	14	C	120
Glycine max (soybean)	Gly m 1.0101; HPS	7.5	P	121
	Gly m 1.0102; HPS	7	P	121
	Gly m 2	8	P	A57106
	Gly m 3; profilin	14	C	AJ223982
Arachis hypogaea (Peanut)	Ara h 1; vicilin	63.5	C	L34402
	Ara h 2; conglutin	17	C	L77197
	Ara h 3; glycinin	60	C	AF093541
	Ara h 4; glycinin	37	C	AF086821
	Ara h 5; profilin	15	C	AF059616
	Ara h 6; conglutin homolog	15	C	AF092846
	Ara h 7; conglutin homolog	15	C	AF091737
Actinidia chinensis (kiwi)	Act c 1; cysteine protease	30	P	P00785
Solanum tuberosum (potato)	Sola t 1; patatin	43	P	P15476
Bertholletia excelsa (Brazil nut)	Ber e 1; 2S albumin	9	C	P04403,M17146
Juglans regia (English walnut)	Jug r 1; 2S albumin		C	U66866
	Jug r 2; vicilin	44	C	AF066055
Ricinus communis (Castor bean)	Ric c 1; 2S albumin		C	P01089
I. Others				
Anisakis simplex (nematode)	Ani s 1;	24	P	A59069
	Ani s 2; paramyosin	97	C	AF173004
Ascaris suum (worm)	Asc s 1;	10	P	122
Den n (red coral)	Den n 1;			Onizuka, p.c.
Hevea brasiliensis (rubber)	Hev b 1; elongation factor	58	P	123,124
	Hev b 2; (1,3-glucanase	34/36	C	125
	Hev b 3	24	P	126,127
	Hev b 4; component of microhelix protein complex	100/110/115	P	128
	Hev b 5	16	C	U42640
	Hev b 6.01 hevein precursor	20	C	M36986/p02877
	Hev b 6.02 hevein	5	C	M36986/p02877

Hev b 6.03 C-terminal fragment	14	C	M36986/p02877
Hev b 7; patatin homologue	46	C	U80598
Hev b 8; profilin	14	C	Y15042
Hev b 9; enolase	51	C	AJ132580/ AJ132581
Hev b 10; Mn-superoxide dismut.	26	C	AJ249148

Ctenocephalides felis felis

(cat flea)

Cte f 1;			
Cte f 2; M1b	27	C	AF231352

Homo sapiens

(human autoallergens)

Hom s 1;	73*	C	Y14314
Hom s 2;	10.3*	C	X80909
Hom s 3;	20.1*	C	X89985
Hom s 4;	36*	C	Y17711
Hom s 5;	42.6*	C	P02538

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Official list of allergens
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MW	Sequence	Accession # or
Allergen source		
kDa	data	References

Systematic and original names

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